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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,324	06/27/2001	Laszlo Prokai	1540/139	2061

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EXAMINER

QAZI, SABIHA NAIM

ART UNIT	PAPER NUMBER
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1616

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,324	PROKAI ET AL.	
	Examiner	Art Unit	
	Sabiha Naim Qazi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 13 November 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>10</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 1-11 are pending. Claims 1-11 are rejected. No claim is allowed. Amendments and request for reconsideration filed in paper no. 9 is hereby acknowledged. Complete reference of the J. Bone Miner Res., filed in IDS paper no. 10 is requested. No conclusion could be drawn by this abstract.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-11 are drawn to compounds and pharmaceutical formulations are examined when the polycyclic compound is a four ring compound, containing alkyl ether group at 17 position of the D ring and A ring is aromatic, such as 1, 3, 5(10) triene-3-ol-17-alkyl ether estradiol. All the rejections are maintained for the same reasons as set forth in our previous office action because arguments are not found persuasive.

Specification

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: See lines 17 and 18 where reference is incomplete. *See page 1.*

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims 1-11 stand rejected under the judicially created doctrine of double patenting over claims 1-29 of U. S. Patent No. 5,554,601 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Instant claims are considered obvious over the US Patent 5,554,601, which assigned to same assignee, University of Florida. Since alkyl ether and 17-position and ring "A" as aromatic ring in the cyclophenantherene ring system is instantly claimed the same invention was patented in the above cited patent. See reasons below in our 103 rejections.

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Claims 1-11 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

What is intended by "**cytoprotective compound**" in claims? Note these are not method or composition claims. It is unclear what is the meaning of "comprising", in claims. Note, that claims are drawn to compounds.

Claims 1-11 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for estradiol, does not reasonably provide enablement for any other steroid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention:

The invention provides a polycyclic compounds having two, three or four carbon rings, the compound also having first end and second end contain alkyl ether group.

The predictability or unpredictability of the art

The unpredictability in the art is very high. The true fact of the state of the art in the steroid area for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study.

The breadth of the claims

The claims are very broad and disclosure does not support the claimed invention.

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The amount of direction or guidance presented

The specification provides no guidance, in the way written description, to use the invention as claimed. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.

The significance of particular compound as broadly claimed in claim 1, different biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study.

The presence or absence of working examples

There are no examples or test data to support the presently claimed invention. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F.2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F.2d 349, 151 USPQ 724.

The quantity of experimentation necessary

Since the nature of the method is so unpredictable, and since there is a lack of guidance present in the specification, the skilled artisan would have to undertake undue experimentation to practice the claimed invention commensurate with the scope of the claims. The skilled artisan, seeking lead compounds for pharmaceutical discovery, would be at a loss as to where to begin such discovery in the absence of such data.

Since the significance of particular estrogen and other compounds for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by

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painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine the utility as presently claimed.

Claims are not limited to the scope to the extent of support in disclosure so that one skilled in the art without undue experimentation can practice invention.

No examples or description of bicyclic or tricyclic compounds are given.

There is no correlation established between the activity of estradiol and other steroid containing A as aromatic ring.

Claims are very broad. Since the nature of the method is so unpredictable, and since the claims are drawn to a broad range of pharmaceuticals, and since there is a lack of guidance present in the specification, the skilled artisan would have to undertake undue experimentation to practice the claimed invention commensurate with the scope of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is improperly dependent on claim 1 because unsaturated alkyl group is not in claim 1. Appropriate correction is required.

Claim Rejections - 35 USC § 102

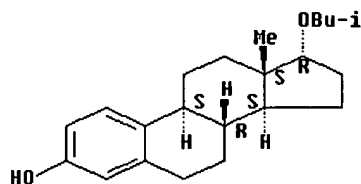
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

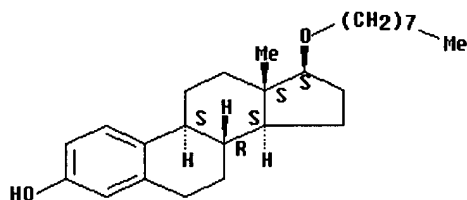
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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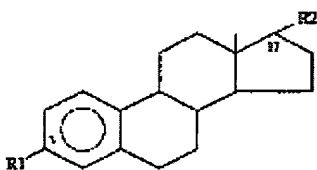
Claims 1-6 rejected under 35 U.S.C. 102(b) as being anticipated by Levchenko et al.. See following compound of RN 119309-39-6.



Presently claimed compounds are represented by



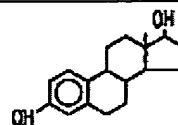
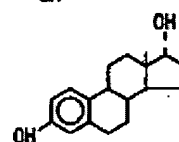
Claims 1-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Simpkins et al. (US 5,554,601). Simpkins et al. teach estro-17 substituted alkyl ether for neuroprotection and method for treating neurodegenerative diseases including Alzheimer's disease, which embraces Applicant's claimed invention. See the entire document especially lines 11-54, col. 3; lines 1-42, col. 4; examples and claims especially claim 4.



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R ₁ AND/OR R ₂ SUBSTITUTIONS	
NAME	STRUCTURE
HYDROXYL	-OH
METHYL	-CH ₃
METHYL ESTER	-OCH ₃
ACETATE	$\text{O}-\text{C}(=\text{O})-\text{CH}_3$
ETHYL ETHER	$\text{O}-\text{CH}_2-\text{CH}_3$
1, 3, (OR 17, 17) DIMETHYL ACETAL	$\begin{array}{c} \text{OCH}_3 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{OCH}_3 \end{array}$
LITHIUM - O	$\begin{array}{c} \text{C}=\text{O} \\ \diagup \\ \text{O}^- \end{array}$
BENZOATE	$\text{O}-\text{C}(=\text{O})-\text{C}_6\text{H}_5$
BENZYL ETHER	$\text{OCH}_2-\text{C}_6\text{H}_5$
GLUCURONIDE	$\text{C}_6\text{H}_4\text{O}_6$
GLUCURONIDE, SODIUM SALT	$\text{C}_6\text{H}_4\text{O}_6\text{Na}$
OXIDE	=O
VALERATE	$-\text{C}_5\text{H}_9\text{O}_2$
CYCLOPENTYLPROPIONATE	$-\text{O}-\text{C}(=\text{O})-(\text{CH}_2)_2-\text{C}_5\text{H}_9$
PROPIONATE	$-\text{O}-\text{C}(=\text{O})-(\text{CH}_2)_2$
HEMISUCCINATE	$-\text{C}_4\text{H}_4\text{O}_3$
PHALPHATE	$-\text{C}_{12}\text{H}_{15}\text{O}_7$

R ₁ AND/OR R ₂ SUBSTITUTIONS	
NAME	STRUCTURE
SODIUM PHOSPHATE	$-\text{O}-\text{PO}_3\text{Na}_2$
ENANTHATE	$-\text{C}_7\text{H}_{12}\text{O}$
GLUCURONIDE, SODIUM SALT	$-\text{C}_6\text{H}_8\text{O}_6\text{Na}$
STEARATE	$-\text{C}_{18}\text{H}_{34}\text{O}$
TRIETHYL AMMONIUM SALT	$-\text{N}-(\text{C}_2\text{H}_5)_3$
CYPIONATE	$\text{O}=\text{C}-\text{CH}_2\text{CH}_2-\text{C}_5\text{H}_9$

17 β ESTRADIOL17 α ESTRADIOL

Instant claims are drawn to 17-substituted alkyl ether at D ring in a compound having aromatic ring A.

Instant claims differ from the reference by reciting specific species and/or a more limited subgenus than the reference. See formula in col. 4 and Figs 9A and 9B on sheets 9 and 10 where various substituents at R₁ and/or R₂ are listed, which includes valerate, stearate, and benzyl ether. Arguments that presently claimed invention disclaims methyl ether and ethyl ether at R 17 position, compounds are still considered obvious due to the reason cited above.

Note, that US '601 teaches that "estrogen compound" is defined as any structure described in the 11th edition of "steroids" from Steraloids Inc. and is incorporated as a reference. See lines 50-67 in col. 4. In present application same reference is incorporated. Even though some compounds are disclaimed, other steroids are considered obvious. No criticality of invention is disclosed.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Naim Qazi whose telephone number is 703-305-3910. If attempts to reach the

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examiner by telephone are unsuccessful, the examiner's supervisor, Jose Dees can be reached on 703-308-4628. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

2/7/2003

S. Qazi

SABIHA QAZI, PH.D
PRIMARY EXAMINER